resection at 6 medical centres in Asia and the West. Their multivariable analysis found that male sex, large tumour size, multinodular tumour, high albumin-bilirubin grade and high levels of alpha-fetoprotein in serum were significantly related to early recurrence. They used these 5 risk factors to develop a pre-operative risk prediction model, and then they added the sixth risk factor of microvascular invasion to develop a post-operative model.

We applaud Chan and colleagues for providing the largest study to date that identifies several risk factors for post-resection recurrence in patients with HCC. Their findings echo numerous previous studies investigating preoperative risk factors of tumour recurrence. However, their conclusions may be interpreted with caution in light of the following concerns.

The first concern is that neither risk prediction model includes macrovascular invasion, which several studies have associated with tumour recurrence and mortality.[4–7] HCC with macrovascular invasion is considered advanced disease in EASL[1] and AASLD[2] staging systems, which do not recommend resection because of the high postoperative recurrence rate and poor long-term overall survival. However, 5 of the 6 medical centres in the study by Chan and colleagues allowed patients with macrovascular invasion to undergo hepatic resection.[3] A potential role of macrovascular invasion in post-resection recurrence should be clarified because Chan *et al.* found that rates of macrovascular invasion among the 4 cohorts with more than 500 patients varied widely (0–28.6%), yet tumour recurrence was 39.8–43.0%. This contrasts with several studies showing that the rate of macrovascular invasion varies directly with 90-day mortality.[4–7] It is possible that the results of Chan and coworkers were influenced by their inclusion of the 0–7.7% of patients who died within 90 days of resection.[3] Patients who died within 90 days should not be included in analysis of tumour recurrence or recurrence-free survival.

Again, we have to congratulate Chan and coworkers on this interesting study on predicting early HCC recurrence after resection, which is still a major problem despite significant advances in hepatic resection. Their important work advances our understanding of pre- and post-operative risk factors of HCC recurrence, but it leaves a question unanswered. Which is the most powerful risk factor of HCC recurrence among the 6 variables they examined, together with other conventional variables, including macrovascular invasion, blood transfusion, and extent of hepatectomy? This question should be answered before we can definitively predict HCC recurrence.

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Conflicts of interest
The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions
X.-Y.Z. and J.O. conceived, wrote and reviewed the manuscript.

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Toward the universal scoring system in treatment for patients with hepatocellular carcinoma

To the Editor:
With great interest, we read the article written by Chan *et al.* in a recent issue of "*Journal of Hepatology*".[1] The authors attempted to develop a new set of preoperative and postoperative scoring systems (ERASL) to predict the outcomes of hepatectomy for hepatocellular carcinoma (HCC), using a statistical approach

and validating its prognostic utility in a large international cohort. Their preoperative score demonstrated decent statistical discrimination for 2-year recurrence-free survival (RFS) in their external validation cohort (C-index 0.601–0.672).

Although there is no doubt regarding the importance of preoperative risk assessment, we have several questions. When the authors decided which variables to include in their score using the Cox regression model, they seem to have excluded some variables (alanine aminotransferase, international normalized ratio, positive resection margin *etc.*) from their equation because those variables were not available in their external validation cohort. It seems unlikely that high volume liver resection centers do not routinely collect such common clinical data, both before and after surgery. Can the authors comment on this? Moreover, some of the excluded variables had higher beta-coefficient than variables they decided to include into their equations: such as positive resection margin (1.550) *vs.* microvascular invasion (1.268). Those exclusion processes may bias their models estimates even if the results showed better discrimination when tested. We would like to recommend showing the result of Wald's test in the patients who have those data included; which will tell us the difference between the full model and reduced (what was presented) model.

Second, they used albumin-bilirubin (ALBI) grade in their model which we suspect may decrease their score's predictive utility. ALBI score consists of serum bilirubin and albumin levels, which is then assigned to one of three grades. In the original ALBI paper, cut-offs for ALBI grade were determined arbitrarily; low, medium, or high risk, describing the lowest 25% of risk, medium risk between the 25th and 90th percentile, and the highest 10% of risk, respectively.[2] During the process of converting from a continuous score into categorical grades, this score would discard variance which might be associated with outcomes and thus decrease prognostic power. In the current manuscript, they used ALBI grades despite the fact that they had raw values of serum bilirubin and albumin, which seemed to decrease the prognostic value of variables to us. We would like to ask the authors to perform a sensitivity analysis between models including ALBI grade, ALBI score (as a continuous measure) and raw bilirubin/albumin data. Sensitivity analysis would tell us whether using ALBI grade is the best option or not.

Lastly, we would like the authors to address the indication for liver transplantation. We agree with the authors' inevitable reply that comparing liver resection populations and liver transplantation populations is like comparing apples and oranges. However, in the ERASL-pre group, the high-risk group had a 2-year RFS of only 26.1%. Those numbers seem to be far lower than transplanted patients with HCC. We calculated pre-ERASL score in patients with HCC who underwent a liver transplant using the United States national registry. In the Scientific Registry of Transplant Recipients, the 2-year RFS of each group were as follows; low 89.6%, intermediate 80.2%, and high 68.7%, respectively (Fig. 1). Although detailed analysis would reveal significant differences in clinical scenario, ERASL-pre high-risk patients should be considered as candidates for liver transplant.

Currently, the indications for different treatment modalities in HCC are highly variable and essentially come down to physician choice, according to tumor morphology/biology, patient background and liver function/condition. In the field of liver transplant for HCC, many centers are trying to develop scoring systems to predict postoperative outcomes.[3–5] Given the recent accumulation of knowledge and advances in decision-making tools such as advanced statistical approach and artificial intelligence, we expect to have one scoring system which can give us treatment modality suggestions as well as prognostic predictions for all patients with HCC in the near future.

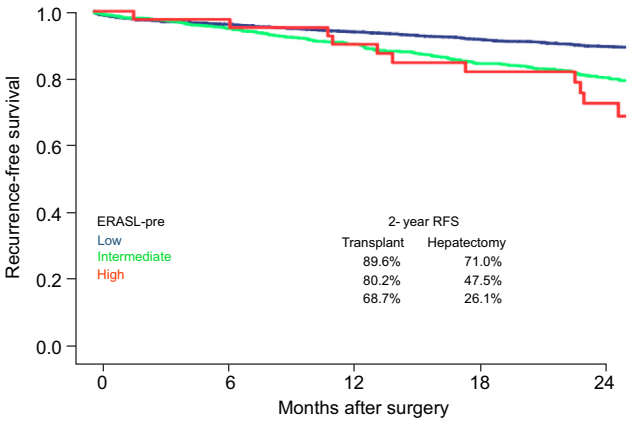

Fig. 1. Kaplan-Meier curves of recurrence free survival according to the ERASL-pre model in patients with hepatocellular carcinoma after liver transplantation in the Scientific Registry of Transplant Recipients. RFS, recurrence-free survival. (This figure appears in colour on the web.)

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Time to recurrence, but not recurrence-free survival, should be the endpoint used to predict early recurrence after HCC resection

To the Editor:
We read with great interest the article by Dr. Chan *et al.*[1] In this study, gender, preoperative albumin-bilirubin (ALBI) grade, preoperative alpha-fetoprotein (AFP) level, tumor size, tumor number, and microvascular invasion were revealed as independent predictors associated with early recurrence after resection of hepatocellular carcinoma (HCC). Using these independent predictors, the authors developed and validated 2 models for predicting early recurrence, *i.e.,* the preoperative model (ERASL-pre) and the postoperative model (ERASL-post). Based on these 2 models, the authors conducted risk stratification to better determine the risk of early recurrence for patients undergoing HCC resection. However, for both model establishment and risk stratification, the authors adopted recurrence-free survival (RFS) as the study endpoint. In terms of the optimal study endpoint and the enrolled clinical variables in this study, we have the following comments:

In the 'Patients and methods' section, the authors defined RFS as "the time from date of curative surgery to the time of recurrence", and "patients with no recurrent disease were censored at the last time at which they were known to be recurrence free". However, the description mentioned above is not the generally-recognized definition of RFS, but always regarded as the definition of time to recurrence (TTR). Actually, in most previous studies, RFS is generally defined as "the time from date of curative surgery to the time of recurrence or death". In other words, if a patient died without recurrence in the follow-up after surgery, it should be considered as an endpoint for RFS but not a censored event. For example, 1 male patient died of decompensated cirrhosis at the 10th month after resection of HCC, but recurrence did not occur at the time of death. For this patient, the RFS should be considered as having an endpoint event (defined as "1"), while the TTR should be considered as a censored event (defined as "0"). Although the time of RFS and TTR is the same (10 months), it was totally different between the 2 final events. We believe that TTR, rather than RFS, may be the optimal study endpoint for predicting early recurrence after HCC resection.

Additionally, what puzzled us was that in this study, ALBI grade, an indicator of hepatic function, was an independent predictor of early recurrence after HCC resection. It is commonly known that early recurrence is most likely the consequence of occult metastasis from the initial tumor, and those aggressive tumor characteristics, including large tumor size, multi-nodularity, poor tumor differentiation, microvascular and macrovascular invasion, and satellite nodules, have been demonstrated to be associated with early recurrence after HCC resection in numerous previous studies.[2–7] Furthermore, in these studies, those characteristics reflecting preoperative hepatic function, such as the Child-Pugh grade, the ALBI grade, and the model for end-stage liver disease score, were always proven to be associated with worse survival rate after HCC resection, instead of early recurrence. Therefore, we wonder if Chan *et al.* used RFS (considering recurrence and death as an end event), but not TTR (only considering recurrence as an end event) as the study endpoint for multivariate Cox-regression analyses in their study.

Last but not least, the authors adopted many clinical variables to set up preoperative and postoperative models for predicting early recurrence before and after surgery, respectively. In most cases, some clinical variables for developing the preoperative model are usually based on preoperative imaging findings, while some clinical variables for developing the postoperative model are often derived from postoperative pathological examinations of specimens.[8–10] The determinations of some clinical variables, including tumor size, tumor number, and gross/macroscopic vascular invasion, would overlap but lead to different results between preoperative imaging findings and postoperative pathological examinations. However, in Chan *et al.*'s study, the analyses of tumor size and tumor number used the same data both before and after surgery. The authors should explain clearly which results the predictive variables, used to develop their 2 models, were based on – the preoperative imaging findings or the postoperative pathological examinations.

In summary, clarification regarding these issues would greatly solidify the conclusions of Chan *et al.*'s study.

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